REMARKS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of two months of the period for response to the outstanding on this case. We enclose our cheque in the amount of the prescribed fees.

The courtesy of the Examiner in granting an Interview on this application to the applicant's representative, Mr. Michael Stewart, and to Mr. Reza Yacoob and Mr. Chris Dahling, members of the Patent Department of the Assignee, Connaught Laboratories Limited, is much appreciated. It is felt that the Interview was material in advancing the prosecution of this application. The Interview Summary Record fairly sets forth the discussion at the Interview. The comments and submissions herein complement and supplement those made to the Examiner at the Interview.

The Examiner noted that the Oath or Declaration was defective and that a new Oath or Declaration in compliance with 37 CFR 1.67(a) identifying the application by application number and filing date is required. The defect arises since Michel Klein did not date the Declaration.

Arrangements are being made to have a Declaration and Power of Attorney re-executed by the inventors and the re-executed document will be forwarded to the Office as soon as practicable.

The Examiner indicated that the lengthy specification had not been checked to the extent necessary to determine the presence of all possible minor errors and requested applicant's co-operation in correcting errors of which the applicants may become aware in the specification. The applicants are currently unaware of any errors requiring correction.

The Examiner rejected claims 22 to 23 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In this regard, the Examiner noted the claims are indefinite because of the use of acronyms like PRP-T, requiring that the acronym must be spelled out when used for the first time in a chain of claims. Claim 22 has been amended to refer to the generic conjugate of a tetanus or diphtheria toxoid and a capsular polysaccharide of *Haemophilus influenzae*, in accordance with page 8, lines 7 to 9.

Having regard thereto, it is submitted that claims 22 and 23 can no longer be considered indefinite and hence the rejection of claims 22 and 23 under 35 USC 112, second paragraph, should be withdrawn.

The Examiner rejected claims 1 to 5 and 24 under 35 USC 102(b) as being anticipated by Barenkamp et al (Mol. Microbiol. 1996). As noted at the Interview, it is believed that the Examiner intended claims 1 to 3, since Barenkamp et al do not disclose a host shock protein (claim 4) nor Hin47 protein (claim 5).

Claim 1 has been amended, as discussed at the Interview, to remove the incidental anticipation by Barenkamp et al by specifying that, in addition to at least one antigen being an adhesin, at least one antigen is not an adhesin. It is apparent that applicant's compositions require both an antigen of *Haemophilus influenzae* which is an adhesin and an antigen of *Haemophilus influenzae* which is not an adhesin. Since both the HMW and Hia proteins of non-typeable *Haemophilus influenzae* are adhesins, it follows that there can be no anticipation of claims 1 to 5 and 24.

Having regard to the revision to claim 1, it is submitted that the rejection of claims 1 to 5 and 24 under 35 USC 102(b) as being anticipated by Barenkamp et al, should be withdrawn.

The Examiner rejected claims 1 to 24 under 35 USC 103(a) as being unpatentable over Barenkamp (WO 87/36,914) in view of Loosmore et al. Much of the discussion at the Interview revolved around this rejection.

The Examiner is correct that Barenkamp teaches high molecular weight surface proteins of non-typeable *Haemophilus influenzae* identified as HMW1, HMW2, HMW3 and HMW4, which are characterized by molecular weight and sequence information.

The reference contains the statement:

> "The present invention provides an immunogenic composition comprising an immunoeffective amount of an active component ... which may be formulated with a pharmaceutically-acceptable carrier therefor". (page 6, lines 20 to 25)

and the further statement:

> "The immunogenic composition of the invention ... may further comprise at least one other immunogenic or immunostimulating material ..." (page 7, ll 1 to 3).

The Examiner asserts:

> "Barenkamp ... teaches complexing additional components to the antigen composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen and others (pp.24-25, lines 7 to 10)."

It is submitted that this characterization of applicants specification takes the relevant passages out of their context. The reference to herpes simplex virus vaccine and pseudorabies virus vaccine (page 24, ll. 19 to 21) are in the context of reporting work performed by Lockhoff (USP 4,855,283) using glycolipid analogs. The references to tetanus toxoid and poliomyelitis virus vaccine (page 24, ll. 28 to 30) are in the context of reporting work performed by Maloney (USP 4,258,029) using OTH. The reference to hepatitis B virus antigen (page 24, lines 31 to 32) is in the context of reporting work performed by Nixon-George et al (ref. 30) using octadecyl esters of aromatic acids. The whole text on page 24, line 8 to page 24, lines 1 to 10, is describing the potential use of certain materials, which have been used with other antigens, as described, with the Barenkamp HMW antigens. There is no suggestion that the HMW antigens be used in conjunction with the recited antigens.

The Examiner further notes that:

> "Barenkamp .... data teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multicomponent non-typeable *H. influenzae* vaccine (page 49, lines 15 to 19)."

However, the cited passage is silent as to what the other components might be, except that they would be components against non-typeable *H. influenzae*.

From the discussion at the Interview, it is apparent that the Examiner relies on these statements for the motivation to combine the references. For the reasons advanced herein, it is submitted no such motivation exists.

The Examiner admits in the Office Action that:

> "Barenkamp ... does not teach the use of a heat shock protein in an immunogenic composition".

In fact, Barenkamp contains no specific teaching of the use of an antigen which is not an adhesin, as recited in amended claim 1, in an immunogenic composition.

As the Examiner states, Loosmore et al teach an analog of *Haemophilus influenzae* Hin47 protein with reduced protease activity. The reference contains the same general statement as Barenkamp:

> "The immunogenic composition of the invention may further comprise at least one other immunogenic or immunostimulating material" (col. 3, ll. 63 to 65).

The Examiner asserts in the Office Action that:

> "Therefore it would have been obvious at the time of applicant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, where one is a high molecular weight adhesin protein, HMW1 or HMW2, since Barenkamp ... teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine and the other component is an analog of Hin47 which is a non-proteolytic heat shock protein with reduced protease activity from *Haemophilus influenzae* as taught by Loosmore et al."

What is lacking from this analysis is any motivation for combining a non-proteolytic heat shock protein of Loosmore et al with the HMW proteins of Barenkamp. There is no motivation provided by Barenkamp to select a non-proteolytic heat shock protein, such as the Hin47 protein analog of Loosmore et al, to be included, along with the HMW proteins, in an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae*.

The Examiner goes on to state:

> "One would expect a reasonable level of success by combining known adhesin proteins and known Hin47 analogs in a multi-component immunogenic composition since Barenkamp ... and Loosmore teach the use [of] these antigens in immunogenic compositions."

The references no doubt describe the use of the antigens individually in immunogenic compositions and describe the generation of an immune response thereto. However, the fact remains that there is no motivation to combine these selected antigens.

In addition, when combining antigens in an immunogenic composition, there is always the possibility of impairing or adversely affecting the respective immunogenicities. In fact, applicants data showed antigenic interference for certain doses and an enhancing effect under other doses (see specification, page 12, line 13 to page 14, line 9). In addition, at dose levels where the HMW and Hin47

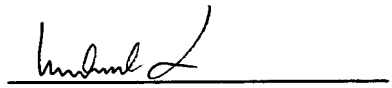
proteins did not improve the immunogenicities, formulating such components with DTP-polio-PRP-T vaccine did not result in any significant synergistic or suppressive effect (see specification, page 14, lines 10 to 23). It is submitted that such results are not predictable from the individual teachings of Barenkamp and Loosmore et al, even if there were a motivation to combine these specific antigens, which, for the reasons advanced above, is not the case.

Having regard to the above, it is submitted that claims 1 to 24 are patentable over the applied art and hence the rejection thereof under 35 USC 103(a) as being unpatentable over Barenkamp (WO 97/36,914) in view of Loosmore et al, should be withdrawn.

The Examiner cited and commented on additional prior art, but did not apply this prior art to the claims. Having regard to the above discussion of the nature of the invention and the distinctions over the prior art, it is submitted that a discussion of such prior art is required.

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,



M.I. Stewart
Reg. No. 24,973

Toronto, Ontario, Canada,
(416) 595-1155
FAX No. (416) 595-1163